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ON THE REACTION OF INDOLE WITH SODIUM BOROHYDRIDE IN FORMIC ACID[1]

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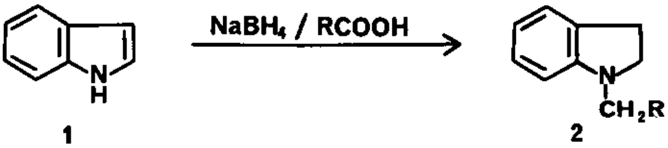
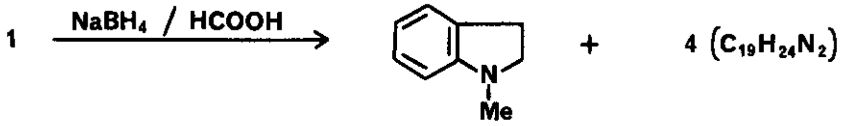
Abstract - The reaction of indole (1) with sodium borohydride in formic acid yields N-methylindoline (3) and a product derived from "indole dimer", 3-(2-(2-N,N-dimethylaminophenyl)ethyl)-1-methylindoline (4), whose structure is proved by independent synthesis.

Several years ago we reported[2] the novel reaction of indole (1) with sodium borohydride ($NaBH_4$) in neat carboxylic acids. This reagent combination effects reduction of the indole double bond and N-alkylation, affording an excellent one-flask synthesis of N-alkylindolines (2).



But in contrast to the other carboxylic acids studied,[2] formic acid, in addition to its more vigorous reaction with $NaBH_4$, gave somewhat erratic results and invariably produced another product, in addition to the expected N-methylindoline (3). In this paper we describe the structure of this by-product.

Thus, treating a solution of 1 (8.5 mmol) in 97% formic acid (45 ml, redistilled) under nitrogen at 0-5° with $NaBH_4$ pellets (75 mmol) (Ventron), followed by a standard work-up[3], gives a mixture consisting of two major products by thin layer chromatography. Column chromatography (basic alumina, hexane elution) gives 3 in 16% yield, identical (TLC, IR, ^1H-NMR, UV) to a sample prepared[4] from N-methylindole, and 4 (oil; crystallizes in freezer) in 32% yield, having the molecular formula $C_{19}H_{24}N_2$ by mass spectrometry (m/e = 280.1923; calcd m/e = 280.1939).



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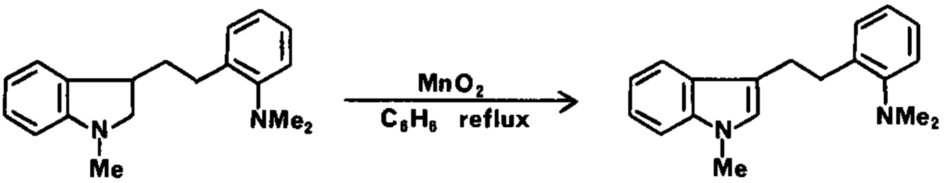
The UV spectrum (95% EtOH) of 4 (217, 252, 296 nm) is very similar to that of 3 (212, 253, 300 nm) and the IR spectrum ($CHCl_3$) of 4 is similar to that of 3, showing strong bands at 2960-2810 (C-H stretch), 1610, 1490, and 1450 (phenyl C=C stretch) cm^{-1}, but no N-H absorption. The ^1H-NMR spectrum of 4 reveals singlets at δ 2.65 (6H; N-Me) and 2.70 ppm (3H; N-Me) and multiplets between 2.3-3.5 (7H) and 6.4-7.4 ppm (8H).

Further structural information on 4 was obtained by treating it with activated manganese dioxide, a reagent known to oxidize indolines to indoles[5]. This gives 5 (oil; 87% yield) which displays 1,3-dialkylindole UV absorption (226, 289 nm) and a mass spectrum consistent with $C_{19}H_{22}N_2$ (m/e 278 (21%), 144 (100%), 134 (9%)). The ^1H-NMR spectrum of 5 shows singlets at δ 2.60 (6H; N-Me), 3.00 (4H; CH_2CH_2), and 3.55 ppm (3H; N-Me), and multiplets at 6.8-7.3 (8H) and 7.5 ppm (1H; indole H-4).

All of these data and mechanistic considerations (*vide infra*) suggest 3-(2-(2-N,N-dimethylaminophenyl)ethyl)-1-methylindoline as the structure of 4 and 3-(2-(2-N,N-dimethylaminophenyl)ethyl)-1-methylindole as the structure of 5.



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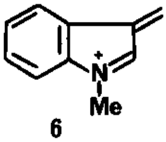
The two very conspicuous peaks in the mass spectrum of 5, m/e 144 (100%) and 134 (9%), can be ascribed to fragment ions 6 and 7, respectively.



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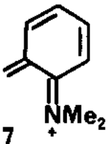

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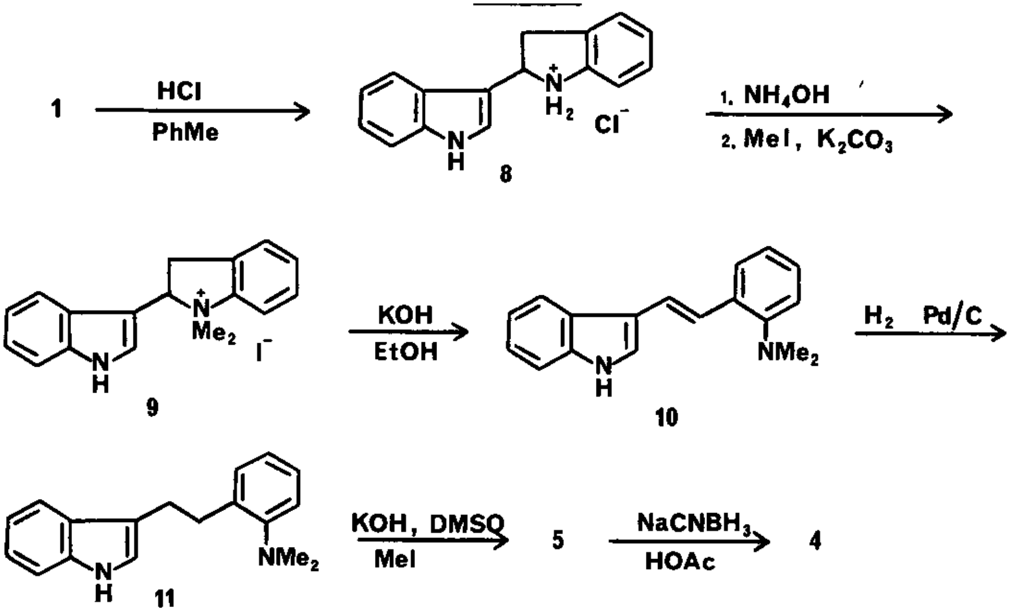
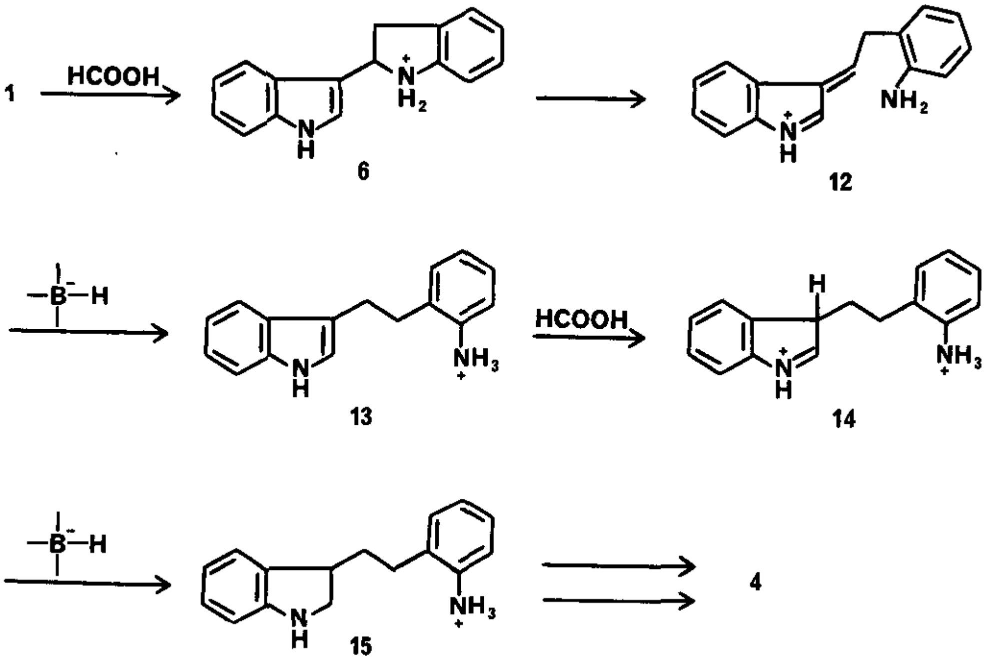
To confirm 4 as the structure of this by-product, we independently synthesized this compound as shown in Scheme I. Dimerization of 1 to the well-known "indole dimer" hydrochloride[6] (8) (88% yield) was followed by conversion to methiodide 9 using a procedure modified from that reported.[7] Thus, slowly adding a benzene solution of the free base of 8 to a refluxing benzene solution of excess methyl iodide in the presence of potassium carbonate gave 9. This crude material was subjected to a Hofmann degradation as previously described[7] and the resulting 3-vinylindole (10) was hydrogenated[8] to 11 (35% yield from 8). Selective indole N-methylation of 11 was readily accomplished[9] to give an oily product (50% distilled yield; bp 165°/ 0.075 torr) that was identical (TLC, IR, ^{1}H-NMR, UV) to 5, as prepared above from 4. Reduction[4] of this material gave a product (93% yield) which was identical (TLC, IR, ^{1}H-NMR, UV) to 4, as obtained from 1. Thus, the structure of 4 is secured as proposed.

Scheme I



A plausible pathway for the formation of 4 is depicted in Scheme II. Formation of the indole dimer 6 (as its formate salt) is followed by an acid-induced gramine-type cleavage[10] to give 3-alkylideneindolenine (12), which is reduced to indole (13) by a presumed[11] formoxyborohydride species. Intermediate 12 has been implicated in the formation of an indole trimer from indole (1) and indole dimer 6.[12] Subsequent protonation of the indole double bond in 13 and reduction of the protonated indolenine (14) lead to indoline (15). Finally, triple N-methylation[3] by the presumed formoxyborohydride reagent would give the bis-tertiary amine (4).

Scheme II



Further studies are needed to understand the difference between formic acid and the other carboxylic acids in their reactions with $NaBH_4$.

Acknowledgments

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References and Notes

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